LIPID METABOLISM AND ATHEROSCLEROSIS*

The Ludwig Kast Lecture

AARON KELLNER

Director of Central Laboratories and Assistant Professor of Pathology, The New York Hospital-Cornell Medical Center

ARTERIOSCLEROSIS has until quite recently been regarded in the same frame of reference as the phenomena of aging, the implicit assumption being made that just as all living creatures pass inevitably from a period of growth and maturation into one of senility and decay, so too the vascular channels harden and wear out.[1] Hence, the degenerative changes in blood vessels came to be looked upon as the natural and inexorable sequelae of life, the price that human tissue paid for prolonged survival. Indeed, the acceptance of arteriosclerosis as a natural process, susceptible to neither remedy nor prophylactic, was for many years responsible for retarding fruitful investigations into its etiology and pathogenesis. It was not until the third and fourth decades of the present century that it became increasingly plain from clinical, morphological, and experimental observations that arteriosclerosis constituted more than a single morbid process, and furthermore, that its most serious manifestations were not essential concomitants of aging[1, 2] but represented rather an acquired abnormality, in Aschoff's words, a disease process "superadded to the process of aging."[3] This change in concept was an important one, for it came at a time when the infectious diseases had in large part been mastered and when diseases of the heart and blood vessels were becoming foremost among the afflictions of mankind; and it was soon to have a stimulating influence on thought and experiment in the field of vascular disease.

NOSOLOGICAL AND MORPHOLOGICAL CONSIDERATIONS

The imperfections of nomenclature have often proved a source of

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confusion and irritation in medicine, and to this the term arteriosclerosis is no exception. Coined by Lobstein in 1833, it is a generic term applied to a group of vascular diseases characterized morphologically by hardening of the vessel wall, and includes such heterogeneous conditions as atherosclerosis, Mönckeberg's or medial sclerosis, arteriolosclerosis, and the age-changes that do occur in blood vessels. In addition to embracing a diversity of clinical and pathological states, the term arteriosclerosis lays undue emphasis upon the hardening aspect, a feature that is scarcely an adequate criterion for estimating the severity of change within the artery wall, for hardening per se is a relatively benign process which produces little if any interference with the flow of blood. Thus, for example, Mönckeberg's sclerosis which leads to widespread and often confluent calcification of the media, particularly in the extremities, rarely impinges upon the calibre of the lumen unless it is complicated by other processes. Likewise, the changes that occur with age in the walls of blood vessels (and blood vessels like other tissues are susceptible in some measure to the ravages of time) consist primarily of loss of elasticity with resultant dilation and tortuosity,[4, 5] a phenomenon that is plain for all to see in the corkscrew temporal arteries exhibited by many individuals past the age of forty, and one that does not compromise the lumen or embarrass the flow of blood. Atherosclerosis, on the other hand, is vastly more serious, for it is characterized not so much by hardening of the vessel wall as by narrowing or obliteration of the lumen. This is an occlusive disease that affects the nutrient vessels of the heart or brain or kidney, and by progressively choking off the flow of blood, leads to functional alteration and, all too commonly, to disability and death. It is with atherosclerosis that we will be concerned in the ensuing presentation.

In the absence of more precise knowledge of its etiology and pathogenesis, atherosclerosis is for the present best defined in morphological terms, its distinctive and fundamental feature being the presence of stainable lipid within the lesion. The earliest recognizable lesions of atherosclerosis, of which the fatty flecks or streaks commonly present in the aorta even in childhood are a typical example, are made up of small focal collections of lipid, sometimes free though usually in foamy macrophages, just beneath the endothelium. These minute intimal cushions project only slightly into the lumen, and offer little or no hindrance to the flow of blood; indeed, they may at this stage even be reversible. It is noteworthy that the endothelium overlying the area of initial involvement is almost always structurally intact – a fact that speaks strongly against the hypothesis that injury to the intima is the primary pathogenetic event. As the process continues, the lesions increase progressively in size and number and often coalesce to form large lipid-rich intimal plaques that gradually begin to encroach upon the lumen. With expansion of the lesions the foam cells in their depths undergo necrosis and disintegrate, discharging their lipid and cellular debris to convert the central portion into a soft, pultaceous mass – the atheroma from which the entire process derives its name. In time, secondary changes become manifest, prominent among which are thickening of the overlying endothelium, disruption of the elastica with invasion of the media, fibrosis, hyalinization, and calcification. Continued enlargement of the lesions leads eventually to serious diminution in the calibre of the lumen, especially in the relatively narrow vessels of the heart and brain, and slowly throttles the flow of blood through these vital channels. Not infrequently, the flow of blood in atherosclerotic vessels, particularly in the coronary arteries, may be halted more abruptly by thrombosis or by hemorrhage into an atheromatous area. These latter events, however, dramatic and lethal though they be, are but complications in the evolution of atherosclerosis. It is to the early and basic lesion – the infiltration of lipids into the intima – that we must turn for clues to the secrets of this morbid process.

Biological and Historical Considerations

Before examining the factors currently thought to be implicated in the causation of atherosclerosis, it would be useful in attaining perspective to touch briefly upon some features of the natural history of this disease. One biological aspect of atherosclerosis that deserves more consideration than it usually receives is the remarkable fact that man is the only mammal in which the disease occurs regularly to any significant degree. To be sure, wild animals in their natural habitat seldom live to old age and consequently might not be expected to manifest extensive atherosclerosis. Many animals, however, have been permitted to live their full life span in scientific laboratories and zoological gardens; furthermore, a great many of them have been carefully examined post mortem, one of the noteworthy studies in this connection being the 10,000 autopsies performed in the Philadelphia Zoo.[6] Analysis of this post-mortem data by Herbert Fox reveals that while medial calcification is frequently encountered in the arteries of various mammals, the lesions of atherosclerosis are exceedingly rare; indeed, clinically significant atherosclerosis is virtually absent. Birds, on the other hand, not infrequently do exhibit considerable atherosclerosis, although the lesions are seldom of sufficient severity to produce symptoms or to cause death. This paucity of significant naturally-occurring atherosclerosis among animals stands in striking contrast to the extraordinary incidence of the disease in man, and provides a challenge for incisive thought and experiment to bring to light the metabolic or perhaps environmental factors that may be involved.

Since atherosclerosis as a serious and fatal disease appears to be limited to the human species, the question then arises whether it is a relatively new disease attacking man in our modern society or whether it has been an affliction of mankind from the days of antiquity. In the case of most diseases the answer to such a question would hinge upon the interpretation of a reference in Scripture or ancient legend; in the case of atherosclerosis, however, a clear answer is provided in one of the most intriguing chapters in the history of medicine. Some 40 years ago archeologists working in the valley of the Nile unearthed hundreds of mummies dating back more than 1500 years before the Christian era, and many of these were in such an excellent state of preservation, due to the favorable influences of a dry climate and the embalming procedures practised by the ancient Egyptians, that it was possible to remove portions of the aorta and other major vessels and to prepare remarkably good histological sections from them. Extensive studies of the arterial lesions of Egyptian mummies by Ruffer[7] and by Shattock[8] make it plain that atherosclerosis was a very common disease 3,000 and more years ago and that the morphological character of the lesions, their distribution, and severity differed in no way from those seen post mortem today. Man, it appears, has been a victim of atherosclerosis for thousands of years; and if, as some think, the anxieties and tensions of modern life contribute heavily to the causation of atherosclerosis, it would seem that the builders of the pyramids were in their time as much a prey to anxieties and tensions as are the splitters of the atom today.[9]

It is relevant to inquire whether such factors as race, age, or sex influence man's susceptibility to atherosclerosis. The question of racial differences cannot be answered definitely at the present time. Atherosclerosis is said to be a relatively mild and infrequent disease amongst certain oriental peoples, the Chinese and Okinawans for example, and attempts have been made to correlate the observation with hereditary or dietary factors, the low consumption of fat and cholesterol-containing foods among those peoples being the distinction most often stressed.[10, 11] The data, however, must be scrutinized with care, since vital statistics in those countries are incomplete and not entirely reliable, and also, since the average life expectancy in those lands is so much shorter than it is in Western countries that figures for the incidence of diseases such as atherosclerosis and cancer, which require many years for their full development, are not really comparable. The evidence, therefore, for the existence of important racial differences must be regarded for the moment as not completely convincing. The role of heredity, on the other hand, has been well substantiated. For the extensive family studies of Wilkinson[12] and of Adlersberg[13] have demonstrated the existence of fairly common genetically transmitted abnormalities of lipid metabolism that are associated with the frequent and early development of clinical atherosclerosis; and conversely, it is well known that there are families that are singularly long-lived and relatively free from the disease.

The part played by age in the genesis of atherosclerosis has been much discussed. It is now generally agreed that though atherosclerosis is not a necessary result of "the wear and tear of life," it is indirectly related to the aging process in the sense that it is a cumulative and slowly progressive disease that becomes increasingly manifest with the passage of time. The lesions of atherosclerosis are frequently encountered early in childhood and, as a rule, their extent and severity become more prominent with advancing age. Though virtually no one is completely free from the mark of the disease, it is, nevertheless, striking to observe on occasion how slight may be the degree of atherosclerosis even in extremely aged individuals. The almost universal prevalence of the disease, coupled with the fact that advanced calcified and eroded lesions are regularly encountered in association with fresh, soft, lipid-rich lesions has led to the concept of atherosclerosis as an episodic disease.[14] Thus, at irregular intervals throughout life, if the proper conditions are present (and they appear to be present to some extent in most of us), clusters of lesions are formed which then slowly undergo degenerative or perhaps even some retrogressive changes, to be followed at some future date by a repetition of the cycle, so that at the end of life there is revealed to the pathologist's eye as an end result the sum total of these additive insults to the vascular tree.

When compared with the male, the female of the human species leads a charmed life with respect to atherosclerosis. Serious coronary artery disease, for example, is remarkably rare in females under age 40, though it is not at all uncommon in the young male, and the decreased susceptibility of the female to the disease is maintained consistently even in the later decades of life, but to a somewhat lesser degree. This freedom from atherosclerosis enjoyed by females is, of course, only a relative one, for they do develop atheromata that are identical in morphology and location to those seen in the male, but at each age level the severity of the lesions in the female, as well as the clinical consequences thereof, are distinctly less marked.[15] It is only when they suffer from diabetes or hypertension that females manifest a degree of atherosclerosis comparable to that of the male. It may be noted, parenthetically, that the advantage possessed by the "weaker" sex with regard to atherosclerosis is in large measure responsible for the fact that as a group they can look forward to decidedly greater longevity than males.

Lipids in Atherosclerosis

The concept that atherosclerosis is fundamentally a disorder of lipid metabolism derives from several sources: first, the demonstration by morphological and chemical means that the lesions themselves contain abundant lipid; second, the oft-made clinical observation that disease states characterized by abnormally high blood lipids are frequently associated with premature atherosclerosis; and third, and perhaps most important, the production of atherosclerosis in animals by experimental procedures that disturb their lipid balance.

It was appreciated by Virchow almost a century ago on morphological grounds that lipids are a prominent constituent of atheromatous plaques.[16] More precise chemical studies by Windaus,[17] Schönheimer,[18] and others[19, 20] have since shown that the lesions of atherosclerosis are rich in cholesterol and cholesterol esters, while containing in addition an admixture of other lipids, notably phospholipids and neutral fat. Indeed, the lipid composition of early atheromatous plaques is so similar to that of blood plasma as to suggest that the atheromatous lipids are in fact derived from the plasma. There was, however, no direct confirmation of this view until quite recently, when it was demonstrated that radioactive cholesterol administered to animals can be detected in the atheromatous foci,[21] and further, by studies which show that under normal conditions the endothelium is permeable to a considerable portion of the plasma lipids.[22] The concept that plasma lipids stream through the endothelium and, under certain conditions to be discussed presently, leave behind a fatty sludge is a basic one in present-day understanding of the pathogenesis of atherosclerosis, and has been aptly and colorfully termed the "delta theory."[23]

Clinicians have long sensed that there is some causal connection between lipid metabolism and atherosclerosis because of the frequent observation that patients with diabetes, xanthomatosis, hypothyroidism, and nephrosis, who exhibit marked hypercholesterolemia, are prone to develop severe atherosclerosis and often at a relatively early age. Moreover, study of selected groups of patients with coronary occlusion and myocardial infarction reveal that in general they have blood cholesterol levels that are considerably higher than the normal, and also, that the cholesterol levels of such individuals tend to fluctuate between wider than normal limits.[24, 25] On the other hand, the picture is blurred by the fact that the vast majority of people presumably developing atherosclerosis have blood cholesterol levels that fall within the accepted normal range. Indeed, numerous investigations have been unable to demonstrate that an elevated blood cholesterol level is an essential prerequisite to the development of atherosclerosis.[26-28] The normal range of blood cholesterol, too, has been, and to an extent still is, a much debated question. In most clinical laboratories the normal figures usually cluster about 200 mg./100 cc., though some workers regard levels up to 350 mg./100 cc. as being within the normal span. In this connection, Gould[29] has pointedly observed that, when compared to the very much lower levels for blood cholesterol normally present in most animals, even a figure of 200 mg. may be considered excessive, and he puts forward the disturbing suggestion that our so-called normal figures may actually represent a state of chronic hypercholesterolemia.

The evidence that atherosclerosis is causally related to a disturbance of lipid metabolism rests in large measure upon studies of the disease in experimental animals, notably those concerned with cholesterol-induced arterial lesions in rabbits, though in some quarters these studies have been unthinkingly maligned and their true significance minimized. In 1913 Anitschkow[30] made the startling discovery that if rabbits are fed one-half to one gram of cholesterol per day they soon manifest striking elevations of blood cholesterol, and, after some weeks, develop intimal lesions of the aorta and other major arteries that in morphology and lipid content bear a remarkable resemblance to the naturally-occurring lesions encountered in human beings. To be sure, there are some differences between the experimentally-induced disease in rabbits and that seen in man; these involve chiefly differences in distribution, the lesions being more prominent in the thoracic aorta and pulmonary artery in the rabbit, whereas in man the abdominal aorta is more severely affected and the pulmonary artery spared; and also the fact that the arterial lesions in the rabbit are almost invariably associated with sustained hypercholesterolemia and are usually preceded by the deposition of lipid in the reticulo-endothelial system and other viscera.[31] The major objection to these experiments is based on the assumption that the rabbit being an herbivorous animal lacks metabolic facilities to handle cholesterol, a substance normally foreign to its diet, and consequently, when this foreign material is included in the diet, it is precipitated in various organs and blood vessels. This cogent argument was utilized effectively by those who felt that observations made on atherosclerosis in rabbits were not transposable to the disease in human beings. During the past few years, however, the ground on which this objection was founded has been largely cut away. In 1942, Dauber and Katz[32] succeeded in producing atherosclerosis in the chick, an omnivorous animal, by adding supplementary cholesterol to the diet; and subsequently, Kendall and his associates[33] produced atherosclerosis in the dog, a carnivorous animal, by suppressing thyroid function with thiouracil and adding cholesterol to the diet. Furthermore, recent studies employing isotopic tracers have demonstrated beyond doubt that, herbivorous though they be, rabbits are capable of synthesizing and metabolizing large quantities of cholesterol.[21, 34] It would appear from the accumulated evidence, therefore, that the cholesterol-induced arterial lesions in rabbits, and also those in the chick and the dog, while perhaps not precise counterparts of the atherosclerosis of human beings, are nevertheless so similar as to suggest the operation of closely allied, if not identical, pathogenetic factors. Yet the mechanism whereby cholesterol feeding induces atherosclerosis in the experimental animal remains undisclosed, and a number of facts make it seem doubtful that elevated blood cholesterol is alone responsible for the development of the disease.[35]

At this point we must digress momentarily to survey the rapid advances in lipid chemistry made possible quite recently by the availability of elegant new tools and techniques – heavy water, radioactive isotopes, electrophoresis, and the ultracentrifuge, to mention but a few. It has become apparent that cholesterol, once considered to be chemically inert and metabolically inactive, is an essential constituent of the mammalian cell and an extremely active metabolite. The evidence is now clear that many tissues can synthesize cholesterol both in vivo and in vitro from simple and readily available precursors such as acetate radicals;[29, 36] that there is a surprisingly rapid interchange between the cholesterol of plasma and that of the liver and other tissues;[29] and also, that the organism as a whole has metabolic facilities not alone for excreting but also for breaking down the cholesterol molecule.[37] It is estimated that human beings may synthesize as much as 1500 to 2000 mg. of cholesterol per day,[29] an amount, it is worth noting, far in excess of the average dietary intake. Similarly, evidence is now at hand for synthesis and active metabolism of the phospholipids and fatty acids, though it would take us far afield to catalogue in detail these and other impressive advances in lipid chemistry.

One area of investigation, however, concerned with the question of lipid transport, is germane to our central theme, for the progress made in this field quickly enriched our understanding of atherosclerosis. A problem that has long perplexed chemists and biologists is the mechanism whereby blood plasma, essentially an aqueous medium, can maintain in exquisitely clear solution so large a quantity of lipid, since there are normally in each 100 cc. of plasma some 500-800 mg. of cholesterol, cholesterol ester, phospholipid, and neutral fat – all compounds which in their pure state are virtually insoluble in aqueous media. Light has recently been thrown on this problem by the work of Boyd,[38] confirmed and extended by Ahrens and Kunkel,[39] which points to the phospholipids as being important in maintaining the stability of the plasma lipids; these workers have demonstrated that plasma remains clear even at abnormally high cholesterol and neutral fat concentrations so long as the phospholipids are concomitantly elevated, whereas the emulsion is unstable and the plasma appears milky if the relative phospholipid content is low. Still more recently, certain plasma proteins have been found to be intimately concerned in the process. This relationship was first hinted at by the imaginative studies of Macheboeuf;[40] it has been enlarged and placed on a firm and quantitative basis by investigations made in the laboratories of Tiselius in Sweden[41] and Cohn in this country.[42] From these studies it now seems probable that the bulk, if not all, of the plasma lipids are present in combination with protein. Indeed, Oncley and his coworkers[43] have elaborated chemical techniques for the separation of two lipoproteins from human plasma, identified electrophoretically as alpha and beta globulins, which between them contain almost all the plasma lipids, and further, the beta-lipoprotein has been purified and found to be soluble in aqueous media despite the fact that it is composed largely of lipid. How these important new facts concerning lipid transport bear upon the problem of atherosclerosis will appear as we scrutinize some recent observations made on the disease in experimental animals and in man.

It has been noted by several groups of workers[44, 45] that in normal rabbits the blood phospholipid level is usually somewhat higher than the cholesterol level, whereas in cholesterol-fed rabbits with atherosclerosis, this situation is reversed, the blood cholesterol level being regularly much higher than the phospholipid. In view of the part played by the phospholipids in stabilizing the serum lipid emulsion, it was suggested that this disparity between cholesterol and phospholipid might be an important factor in the development of experimental atherosclerosis. A means of testing this hypothesis became available when it was found that certain surface-active agents when injected intravenously produced, among other things, marked and sustained elevations of the blood phospholipid content.[46] Accordingly, an experiment was performed in which rabbits fed a high-cholesterol diet were given repeated intravenous injections of the surface-active agents Tween 80 or Triton A-20. The injected animals developed far less atherosclerosis than did uninjected control animals fed the same cholesterol diet, and it is of interest that the degree of atherosclerosis could be correlated with the blood phospholipid level; the injected animals had high phospholipid as well as high cholesterol levels, in sharp contrast to the controls in which the cholesterol levels were comparably elevated but the phospholipid levels distinctly lower.[47] Similar findings have now been reported by Duff and his colleagues,[48] who also found that the protective effect of alloxan diabetes against the development of cholesterol-induced atherosclerosis in rabbits, previously discovered by them, could be correlated with elevated phospholipid and neutral fat levels.[49] Moreover, the clinical studies dealing with blood phospholipids done by Ahrens[50] in patients with biliary obstruction, those of Gertler[51] in patients with coronary artery disease, and those of Eilert[52] in women receiving estrogenic hormone therapy, though not conclusive, do suggest that the cholesterol-phospholipid ratio may be a factor in the atherosclerosis of human beings as well. These clinical and experimental findings serve to focus attention upon the physico-chemical state of the blood lipids and upon the interrelations between the various lipids, rather than upon the absolute level of the blood cholesterol, as being important determinants involved in the pathogenesis of atherosclerosis.

During the past two years the picture has acquired more detail with the appearance of the ingenious and provocative studies of Gofman and his associates[53, 54] These investigators using the analytical ultracentrifuge found that all the major lipids in the serum are transported in the form of giant lipid-protein complexes which can be characterized and quantitated by their ultracentrifugal flotation properties. The pattern of these lipoprotein molecules, though differing widely from one individual to another, is quite constant under normal conditions for any one individual during prolonged periods of time, and is subject to modification by diet, disease, and certain drugs. While these complexes are more common in hypercholesterolemic sera, they may, and very frequently do, occur in the sera of patients with normal or even low cholesterol levels. Further, these workers observed that one portion of the spectrum of these large lipoprotein aggregates, those classified in the S_f 10-30 category, are regularly associated with the development of experimental atherosclerosis in cholesterol-fed rabbits, and similarly, the molecules in the S_f 12-20 range appear to bear a strong correlation to the development of the disease in human beings. Comparison of a large group of normals with a matched group who had suffered myocardial infarction reveals a significantly greater incidence of excessive concentrations of these abnormal molecules in the sera of the latter group. Moreover, these workers maintain that the level of S_f 12-20 molecules in the blood may serve to designate, years in advance of its clinical manifestations, those who are susceptible to severe atherosclerosis, and may be useful as a means of estimating prognosis and evaluating therapy following myocardial infarction. It is noteworthy that females, especially in the early and middle age groups, have in their sera far lower concentrations of these molecules than do males, a fact which may account for their relative freedom from clinical atherosclerosis. Graham, working in Gofman's laboratory, has recently reported[54] that injection of heparin into human beings and experimental animals brings about a dramatic reversal toward normality in the serum lipoprotein picture, and that repeated injections into rabbits protects them against the atherosclerosis of cholesterol feeding. It is of interest that the effect of heparin is apparently unrelated to its anticoagulant action. This intriguing observation, quite apart from its possible therapeutic implications, may provide a clue to understanding the metabolic relations involved in the formation of lipoprotein complexes. Despite the recognized difficulties of quantitating atherosclerosis in human beings – for neither clinical, radiographic, nor even post-mortem estimates are wholly reliable – and despite the acknowledged pitfalls in finding an adequate control series for a disease which is practically universal, it must be stated that the association between the serum concentration of these large lipoprotein molecules and the development of severe atherosclerosis is more impressive than any that has hitherto been demonstrated. Whether these molecules are themselves the offending agent in atherosclerosis or whether they represent an epiphenomenon, a reflection of a more ultimate cause, remains to be determined. It is nevertheless becoming increasingly clear from these researches, and from the parallel studies of Barr, Russ and Eder[55] using chemical techniques to fractionate plasma lipoproteins, that in atherosclerosis there is an underlying lipid metabolic defect, one of the manifestations of which is an aberration of lipid transport which appears to promote the deposition of lipid within the intima of blood vessels.

Attention has been drawn for a long time to the possible role of dietary factors in the causation of atherosclerosis. The question has frequently been raised whether over-abundant diet, rich in fatty and cholesterol-bearing foods, may not be responsible for the alarming incidence of atherosclerosis in our society. In brief, are we eating our way to atherosclerosis? A decisive answer to this question is not forthcoming at the present time. The post-mortem studies of Wilens[56] and the experimental observations of Firstbrook[57] point to a correlation between overnutrition and atherosclerosis. The level of blood cholesterol, though little influenced by moderate fluctuations in the cholesterol or fat content of the diet,[58] may be appreciably reduced by rigid restriction of both, as in the rice diet. [59, 60] It is a curious fact, however, that addition of vegetable fat containing no cholesterol to such a severely curtailed diet causes a return of the blood cholesterol to previous levels, making it plain that elimination of cholesterol-containing foods from the diet is not effective unless the total fat content of the diet is stringently reduced at the same time.[58, 61] It has been pertinently said of atherosclerosis that if cholesterol is the culprit, fat is an active accomplice.[62] Gofman has studied the effect of diet on the lipid transport mechanism, and he has reported a decrease, and on occasion even disappearance, of the S_f 12-20 lipoprotein molecules from the blood of individuals placed on diets of low fat and low cholesterol content.[54] Such diets have in fact been advocated as having beneficial effects in atherosclerosis, though the evidence for this is still quite incomplete. In connection with dietary factors one must consider the lipotropic agents, especially choline and inositol, which, because of demonstrated effectiveness in reversing the fatty liver of certain nutritional deficiencies and perhaps also because they are essential constituents of the major blood phospholipids, have been advocated and widely employed in the therapy of atherosclerosis.[63] The results of clinical trials, however, are unconvincing; and the use of these agents in experimental animals has repeatedly been found unsuccessful in raising blood phospholipid levels or in affecting appreciably the development or resorption of atherosclerosis.[64-66] Thus, additional clinical and experimental data are required before the role of diet and specific dietary factors in this disease can be accurately assessed.

Lest we become so preoccupied with the chemistry of lipids that we lose sight of the blood vessels where the disease actually strikes, mention must be made of the operation of other factors which, though perhaps ancillary, are nevertheless important in a full understanding of atherosclerosis as a pathological process. It seems quite probable from studies on the permeability of the endothelium that there is a constant flow of plasma filtrate containing lipids and many other substances across the endothelium into the interstices of the vessel wall,[67] whence they are removed via lymphatics or vasa vasorum by mechanisms as yet undisclosed. Interference with these removal mechanisms may well account for the localization of atheromata at sites of injury to the vessel,[68] and also at points of fixation and branching, and, in like manner, may explain the propensity of syphilis to enhance the severity of atherosclerosis in the thoracic aorta.[69] Intravascular pressure is unquestionably another factor in the localization of atheromata, lesions being most common at points of high pressure and scarce or absent where pressure is low. Thus, the systemic arterial tree is most vulnerable, the pulmonary circulation distinctly less so except in instances of pulmonary hypertension, and the veins virtually unaffected by the disease, though, needless to say, the lipid composition of the plasma is essentially the same in all compartments of the arterial and venous channels. That increased blood pressure may also augment atherosclerosis has recently been demonstrated experimentally by Wakerlin.[70] Dogs were made hypertensive by the Goldblatt technique and then fed a diet containing cholesterol and thiouracil; these animals developed atherosclerosis at a strikingly accelerated rate as compared with that of normotensive controls fed the same diet. It should be noted in this connection that dogs with sustained hypertension for many years do not develop atherosclerosis in the absence of the disturbed lipid metabolism induced by the diet. The effect of pressure is thought to derive from increased filtration through the vessel wall, which, if the underlying lipid defect of atherosclerosis is present, serves to hasten the deposition of lipid. It may be that such a mechanism is responsible, in part at least, for the well recognized clinical fact that hypertensives, both male and female, are particularly susceptible to atherosclerosis and its more serious complications.[71]

"Science," Conant[72] has stated, "advances not by the accumulation of new facts, . . . but by the continuous development of new and fruitful concepts." Judged by this standard, substantial progress has been made in our understanding of atherosclerosis. The happenings of the past few years, herein briefly recounted, surely attest to the profound stirring that is now perceptible in this field. Numerous investigators armed with wondrous new tools are probing deeply into the vital chemistries of tissues and cells. An abundance of new facts has been wrested from nature, and based on them there have been erected dynamic and fruitful concepts that bode well for the future and hold much promise for clinician and experimentalist. As a result of these advances, the attitude of hopelessness about the disease is giving way to one of quiet optimism that in atherosclerosis prevention and, indeed, even therapy may be attainable.

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